high [blast crisis]), the effects associated with the homozygous group are similar to the unadjusted results (data not shown). Similarly, after adjusting for number of mismatched HLA alleles (considering HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1, with a range of 0 to 8 total mismatches in the 391 patients), the effects associated with the homozygous group are similar to the unadjusted results (data not shown).

In summary, the absence of functional CCR5 in marrow donors may be associated with less GVHD. With only 8 patients having a homozygous donor, these preliminary results are in need of larger numbers. Therefore, we propose screening the sample repository from the National Marrow Donor Program Foundation to identify additional patients with a CCR5Δ32 homozygous donor. Currently CCR5 antagonists are developed and approved for HIV treatment [10]. Further studies may provide rationale to develop novel treatments for GVHD.

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AUTHORSHIP STATEMENT

Q.M. designed and performed the research. T.A.G. analyzed data. Q.M., T.A.G. and R.F.S. wrote the paper.

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Institution Affects Association between CMV Seronegative Graft and Leukemic Relapse after Pediatric HCT

We read with interest the letter from Travi and colleagues [1] reporting results from their own institution that differed from those we recently published in the *Journal* [2]. The letter inquired whether differing distributions of demographics or conditioning regimens might explain why the similar, contemporary samples yielded contrasting findings on whether donor/recipient cytomegalovirus (CMV) serostatus affects the incidence of leukemic relapse after pediatric hematopoietic cell transplantation (HCT). Here we reply to the question, and offer a potential explanation of our own.

After stating the traditional view, established before the current era of CMV preemptive therapy, that "seronegative recipients with a seronegative donor (D−/R−) have shown an improved outcome" after HCT, Travi et al. [1] reported that, among pediatric recipients at their institution, D−/R− grafts were not associated with improved outcome, either in relapse or nonrelapse mortality (NRM). In contrast, our study of a similar pediatric sample [2] yielded the novel finding that D−/R− grafts were significantly associated with poorer outcome (higher incidence of relapse, inferior relapse-free survival [RFS]) than other grafts. Because relapse was rarely detected by Travi et al. [1] after 2 years posttransplant, we compared 2-year incidence by institution and serostatus, using Figure 1B from Travi et al. [1] and Figure 2 from our article [2]. At 2 years post-HCT, the 2 samples had similar cumulative incidences

of NRM (which did not differ by D−/R− serostatus) and similar cumulative incidences of relapse in the D−/R− subgroup, but at our institution only, recipients of seropositive grafts (D+ and/or R+) had significantly reduced incidences of relapse. We interpret this finding as evidence that certain conditions at our institution promoted the graft-versus-leukemia (GVL) effect of HCT in our pediatric sample, specifically in those recipients who received CMV-seropositive grafts.

What conditions might have differed between our 2 institutions and accounted for the contrasting findings? Travi et al. [1] suggested that the explanation might be found in the distribution of ethnicity (Caucasian versus other), total body irradiation (TBI)-based conditioning, or age in our 2 samples. To address this suggestion, we examined whether the samples differed on demographics or TBI use. We then investigated whether the association between D−/R− serostatus and relapse in our sample became nonsignificant after adjustment for age, TBI, or ethnicity, or was significantly modified by interaction with these characteristics.

Our sample had a higher proportion of Caucasians (86.4% versus 74.3%, $P < .01$), but TBI use was similar (85.0% versus 81.9%) in the 2 samples. Whether they differed in age could not be determined, because Travi et al. [1] did not report an age distribution. In our published model of relapse [2], D−/R− serostatus remained significant after adjustment for age and other covariates; the effect of serostatus did not vary with age. Further analysis determined that TBI use was not associated with relapse and did not modify the effect of serostatus. Non-Caucasian ethnicity was not associated with relapse, but appeared to enhance the effect of serostatus: the cumulative incidence-based hazards ratio of relapse with D−/R− graft was 2.81 (95% confidence interval [CI] 1.25-6.28) in Caucasians and 12.3 (2.94-51.4) in non-Caucasians, compared to recipients of seropositive grafts of any ethnicity. We regard the interaction between serostatus and ethnicity with caution, however, because our sample had few non-Caucasian patients (19/140), a biologic rationale for the interaction is lacking, and the model's fit was not appreciably improved after stratifying seronegative graft by ethnicity. In summary, differences in demographics or TBI use are unlikely to explain why an association between D−/R− graft and relapse was present in our sample but not in that of Travi et al. [1].

We believe that a more compelling explanation for why the 2 institutions obtained different results may be found in their different methods of CMV surveillance. At our institution, surveillance at the time was primarily by viral culture, a less sensitive method than pp65 antigenemia or polymerase chain reaction (PCR), used historically at the other institution [3]. Moreover, the sensitivity of viral culture in our patients may have been further reduced if the volume of blood cultured was less than that typically used for adults. Less sensitive surveillance may have delayed or reduced detection of CMV activation, which in turn, may have delayed or reduced initiation of preemptive therapy. As a result, exposure to subclinical CMV viremia may have been prolonged, and ganciclovir may have been initiated later or less often, among our recipients of seropositive grafts than among similar patients at the other institution. Recipients of seronegative grafts, in contrast, would have been little affected by differences in sensitivity of CMV detection, because viremia is far less common in that group. It is possible that prolonged early exposure to subclinical CMV had a stimulatory effect on natural killer (NK) and T cells [4-7]. It is also possible that delayed or reduced initiation of ganciclovir, a drug that can suppress T cell proliferation [8] and delay T cell recovery [9], benefitted repopulating T cells. Either possibility could have enhanced the GVL effect in our recipients of seropositive grafts.

We agree with Travi et al. [1] that a definitive investigation of the effect of graft serostatus on the outcome of pediatric HCT will require a large, multicenter study. In fact, we formally proposed such a study to the Center for International Blood and Marrow Transplant Research (CIBMTR) in November 2008. It must be recognized, however, that results from a multicenter study will be conclusive only if the analysis controls for differences between centers, and also within centers over time, in the methods of CMV surveillance and CMV management (preemptive therapy, prophylaxis, or both). In addition, the choice of eligibility criteria will be important. For conclusive results, not only should all subjects be pediatric recipients of primary, myeloablative, allogeneic HCT for acute leukemia, but the primary analysis should exclude T cell depleted or cord blood grafts, because in those grafts, the effect of serostatus on incidence of relapse might be abolished.

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Alloimmune Retinopathy Associated with Antibodies to Transducin-α as a Complication of Chronic Graft-Versus-Host Disease

The paraneoplastic retinopathies, first described in 1976 [1], include cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR) [2]. Affected patients present with acute, subacute, or chronic signs and symptoms of retinal dysfunction [3]. Findings on retinal examination include attenuated vessels, "waxy" disc pallor, and retinal pigment epithelial mottling, although at times the exam is normal [4,5], and there are characteristically no signs of inflammation [6]. Electroretinograms (ERGs) are typically abnormal, and negative waveforms are common [3]. Pathogenic retinal antibodies are often found in the serum of affected individuals.

Patients with CAR usually have coexisting solid tumors involving the lung, ovaries, or colon [7]. Serum from affected individuals may contain antibodies to recoverin, a calcium binding protein that controls phosphorylation of rhodopsin in both rod and cone photoreceptors [8,9].

Recently, a series of patients has been identified with antibodies to transducin-α, a 40-kDa photoreceptor G-protein naturally expressed in rods and cones (G. Adamus et al., unpublished data). Visual transducin is activated by rhodopsin following initial photon capture, subsequently activating PDE6, and ultimately photoreceptor membrane hyperpolarization [10]. Transducin is also present in other tissues and associated with tumors, including melanomas and carcinomas [11].

Here, we report the case of a 25-year-old woman found to have new onset retinopathy in the setting of chronic graft-versus-host disease (cGVHD) after allogeneic transplant, with subsequent demonstration of serum anti-40-kDa antibodies that react with retinal transducin-α. To our knowledge, this is the first report of antibodies to transducin associated with retinopathy as a complication of cGVHD.

The patient presented in May 2003 with pancytopenia, and was found to have FAB M4 acute myelogenous leukemia (AML) with a 6;11 translocation. Following successful standard induction chemotherapy and 2 cycles of consolidation, she underwent an HLA-matched, ABO mismatched unrelated donor (MMUD) peripheral blood stem cell transplant (PBSCT) in September 2003. Short-course methotrexate (MTX) and tacrolimus were utilized for GVHD prophylaxis.

In May 2005, early cytogenetic recurrence of leukemia was noted by interphase fluorescein in situ hybridization (FISH). Donor lymphocyte infusion (DLI) was administered twice, followed by reinduction chemotherapy in mid-August 2005. After entering a second complete remission (CR2), the patient underwent a second allogeneic PBSCT in October 2005, from a 10/10 matched unrelated donor (MUD).

Following her second transplant, the patient developed grade III GVHD involving the skin and liver. She was treated successfully with prednisone. A baseline ophthalmologic evaluation in February 2006 disclosed mild exposure keratopathy and buried optic nerve drusen. For persistent pancytopenia, the patient received a CD34-selected marrow boost in May 2006. Subsequent to this, tacrolimus was switched to sirolimus because of hyperkalemia, renal insufficiency, and microangiopathy. Diarrhea developed in August 2006, and after a month of persistent symptoms sirolimus was discontinued, with prednisone and hydroxychloroquine used for GVHD treatment. In March 2007, worsening liver GVHD was successfully treated with daclizumab, rituximab, and IVIg, followed by a return to glucocorticoids and hydroxychloroquine for GVHD control.

The patient was seen by an ophthalmologist in November 2007, and found to have continued